Marked up version of the paragraph on page 43, lines 8-15, through page 44, lines 1-6, is below:

To a solution of poly-glu_{15} **(SEQ ID NO: 8)** (0.600g, 0.310mmol) in DMF (25ml) was added EDCI (2.07g, 10.8mmol). The resulting mixture was allowed to stir at ambient temperature for one hour. Then, N-methyl morpholine (0.51ml, 4.7mmol) was added followed by a mixture of acyclovir (1.74g, 7.75mmol), DMF (25ml) and N-methyl morpholine (0.85ml). The reaction mixture was stirred at ambient temperature for 4 days. After this, water (50ml) was added and all solvent was removed. To the dried mixture was added water (100ml) and a precipitate of unreacted acyclovir formed. Solid was centrifuged and the supernate was purified using ultrafiltration (YM1 membrane). Approximately 300ml water was allowed to pass through the membrane. NMR has shown an unexpected alkyl-urea side chain attached impurity. Poly-glu(acyclovir) (0.970g) was obtained as a light yellow solid: ^{1}H NMR (D_2O) δ 1.11 (br m, 4H, urea), 2.01 (br m, 2H, Glu-β H), 2.39 (br m, 2H, Glu-γ H), 2.72 (br m, 2H, urea), 3.32 (br m, 6H, acyclovir CH_2 and urea), 3.83 (br m, 3H, urea), 4.38 (br d, 3H, Glu-α H), 5.47 (br s, 2H, acyclovir 1' CH2), 7.94 (br s, 1H, acyclovir 8 CH).

Marked up version of the paragraph on page 45, lines 1-13, is below:

To a solution of poly-glu_{15} **(SEQ ID NO: 8)** (0.078g, 0.040mmol) in DMF (5ml) was added EDCI (0.035g, 0.18mmol). After stirring for 30 minutes, N-methyl morpholine was

added (0.03ml, 0.24mmol). After stirring for 10 minutes, a solution of fexofenadine (0.100g, 0.20mmol), N-methyl morpholine (0.07ml, 0.60mmol) and DMF (5ml) was added via a syringe. After stirring reaction at ambient temperatures for three days, sample was dissolved in water (25ml). A solid precipitate formed which was both drug-conjugate and free fexofenadine. Water was acidified and all solids dissolved. Purification using ultrafiltration (YM1 followed by YM3) and size exclusion chromatography using Sephadex-25 at pH 7 yielded poly-glu(fexofenadine) (0.010g) as a white solid: ^{1}H NMR (D_2O) δ 1.37 (s, 8H, fex. CH_2 and CH_3), 1.58 (br m, 5H, fex. CH and CH_2), 1.99 (br m, 24H, Glu-β H), 2.31 (br m, 24H, Glu-γ H), 2.70 (br m, 10H, fex. CH and CH_2), 4.14 (br m, 26H, Glu-α H), 7.25 (br m, 14H, fex. aromatic H).

Marked up version of the paragraph on page 46, lines 4-15, is below:

To a solution of poly-glu_{15} **(SEQ ID NO: 8)** (0.123g, 0.060mmol) in DMF (8ml) was added EDCI (0.403g, 2.10mmol). After 30 minutes, N-methyl morpholine (0.13ml, 1.2mmol) was added. After 35 minutes, a solution of zalcitabine (0.200g, 0.95mmol), N-methyl morpholine (0.10ml, 0.9mmol) and DMF (2ml) was added via a syringe. The resulting mixture was stirred at ambient temperature for 48 hours. Solvent was removed and the residue was dissolved in water (15ml). Ultrafiltration (YM1 followed with YM3) and size exclusion using Sephadex-25 at pH 7 yielded poly-glu(zalcitabine) (0.083g) as a light yellow solid: ^{1}H NMR (DMSO-d_6 w/D_2O) δ 1.14 (br m, 20H, urea), 1.90 (br m, 30H, Glu-β H, Glu-γ H and CH_2 in zalcitabine), 2.66 (br m, 4H, urea), 3.24 (br m, 36H, urea, CH and CH_2 in zalcitabine), 4.29 (br m, 8H, Glu-α H), 5.87 (br s, 1H, zalcitabine 1' CH), 7.18 (br s, 1.19H, zalcitabine NH_2), 8.52 (br s, 1H, zalcitabine 6 CH).

Marked up version of the paragraph on page 57, lines 15-21, through page 58, lines 1-9, is below:

Summary of the synthesis of [Lysine]$_{xx}$ –[Gemfibrozil or Naproxen] or [Glu]$_{xx}$ L-DOPA

Synthesis of **(SEQ ID NO: 8)** [Glu]$_{15}$ - L-dihydroxyphenylalanine or **(SEQ ID NO: 8)** [Glu]$_{15}$ -L-DOPA

L-DOPA (0.050 g, 254 □mol) and GluNCA (0.666 g, 3.85 mmol) were dissolved in 6 ml DMF. After stirring overnight under Argon, the reaction was examined by thin layer chromatography (9:1 H_2O: HOAc) showed some free drug (R_f= 0.70) and a more polar spot presumed to be polymer (R_f= 0.27). The reaction was quenched by the addition of 12 ml H_2O. The pH was adjusted to pH 1-2 using 1N HCl. The solvent was removed by rotary evaporation and the viscous residue dried in vacuum. The resultant syrup was transferred to a new vessel in H_2O and lyophilized. The resulting crystals were off white to light brown. Yield: 0.470 g, 62%. ^{1}H NMR showed pyroglutamic acid contamination; therefore, the material was suspended in H_2O and ultrafiltered (Millipore, regenerated cellulose, YM1, NMWL =1000), and the retentate dried under vacuum. Yield: 0.298 grams. ^{1}H NMR (500MHz, DMSO) indicated a relative ratio of 30:1 Glu:L-DOPA, 6.6 (L-DOPA aromatic), 6.4 (L-DOPA aromatic), 4.1 (Glu, α)
1.85 (Glu, β), 2.25 (Glu, γ, L-DOPA), 2.3 (L-DOPA, benzylic), 12.4-11.5 (Glu, CO_2H), 8.0 (Glu, amide)

Marked up version of the paragraph on page 58, lines 13-16, is below:

Synthesis of **(SEQ ID NO: 9)** [Glu]$_{10}$ –L-DOPA

As in the synthesis of **(SEQ ID NO: 8)** $[Glu]_{15}$-L-DOPA except 0.439 grams of GluNCA were used. The final yield of purified material was 0.007 grams. The ^1H NMR (500MHz, DMSO) indicates 8:1 Glu:L-DOPA.

Marked up version of the paragraph on page 59, lines 6-14, is below:

Synthesis of polylysine-Naproxen

To $[Lys]_{14}$ **(SEQ ID NO: 10)** · 14 · HBr (0.100 g, 35 mmol) in 1 ml of H_2O (containing 10 mg/ml Na_2CO_3) was added Naproxen-Succinimide (0.124 g, 379 mmol) in 2 ml of dioxane. After stirring overnight a precipitate formed. More precipitate was formed by the addition of 30–40 ml of H_2O (containing 10 mg/ml Na_2CO_3), isolated by filtration and washed with 50 ml of Et_2O. The fine white powder was dried (0.095 g, 53%): ^1H NMR (500MHz, DMSO) 8.1 (m, 1H, lysine; amide), 7.8-7.0 (m, 6H, aromatic), 4.4-4.1 (m, 2H, α methine), 3.3 (s, 3H, OCH_3), 2.8 (m, 2H, ε), 1.7-1.0 (m, 9H, β, γ, δ, CH_3).

Marked up version of the paragraph on page 60, lines 5-13, is below:

Synthesis of polylysine-Gemfibrozil

To $[Lys]_{11}$ **(SEQ ID NO: 11)** · 11 · HBr (0.100 g, 43.5 αmol) in 1 ml of H_2O (containing 10 mg/ml Na_2C0_3) was added Gemfibrozil-succinimide (0.094 g, 261.1 αmol) in 2 ml dioxane. After stirring overnight a precipitate formed. More precipitate was formed by the addition of 30 ml of H_2O (containing 10 mg/ml Na_2C0_3), isolated and washed with 50 ml Et_2O. The fine white powder was dried (0.019 g, 1%): ^1H NMR (500MHz, DMSO) 1.5-1.0 (m, 12H, β, γ, δ, CH_3), 1.85-1.5 (m, 4H, CH_2), 2.3, 2.1 (s, 6H, aromatic CH_3), 3.35 (s, 2H, ε),

3.85 (s, 2H, OCH_2), 4.05 (s, 1H, α), 5.6 (d, 1H, carbamate), 7.0-6.7 (m, 3H, aromatic), 8.0 (d, 1H, amide).

Marked up version of the paragraph on page 62, lines 22-25, through page 63, lines 1-6, is below:

T4 Conjugation to preformed homopolymers

To N-TeocT4 (0.017 g, 17 μmol) in 1 ml dry DMF was added dicyclohexylcarbodiimide (0.004 g, 18 μmol). After stirring for 30 minutes N-dimethyl-4-aminopyridine (0.004 g, 36 μmol) and Gly_{18} **(SEQ ID NO: 12)** (0.017 g, 17 μmol) were added and the reaction stirred overnight. The cloudy solution was poured into 20 ml H_2O and extracted twice with 10 ml CH_2Cl_2. The aqueous component was acidified to pH 3 with 1 N HCl and chilled to 4° C. The material was isolated by centrifugation and the pellet thrice washed with 8 ml H_2O. The pellet was dried in vacuum to yield dicyclohexylurea and N-TeocT4-Gly_{18} **(SEQ ID NO: 12)**: ^{1}H NMR (500 DMSO) 7.8 (T4 aromatic), 7.1 (T4 aromatic), 4.1 (α).

Marked up version of the paragraph on page 64, lines 15-16, is below:

Typical preparation of T4 N-capped homopolymers:

T4-Leu_{15} **(SEQ ID NO: 13)**

Marked up version of the paragraph on page 65, lines 1-3, is below:

T4-Phe_{15} **(SEQ ID NO: 14)**

White powder (58%): ^{1}H NMR (360 MHz, DMSO) 7.0-8.1 (NH, aromatics), 4.5 (α), 3.0 (β); MALDI-MS indicates T4-Phe_{1-5} **(SEQ ID NO: 15)**.

Marked up version of the paragraph on page 65, lines 5-7, is below:

T4-Met_{15} **(SEQ ID NO: 16)**

White powder (10%): ^{1}H NMR (500MHz, DMSO) 8.0-8.5 (amide NH) , 4.4 (α) 2.5 (γ), 2.05 (ε), 2.0-1.7 (β).

Marked up version of the paragraph on page 65, lines 9-11, is below:

T4-Val_{15} **(SEQ ID NO: 17)**

White powder (14%): ^{1}H NMR (500MHz, DMSO) 7.75 (T4 aromatic), 7.08 (T4 aromatic), 4.35 (α), 3.45 (β), 1.05 (γ).

Marked up version of the paragraph on page 65, lines 16-22, is below:

To T4-$[Lys(Boc)]_{15}$ **(SEQ ID NO: 18)** (0.256 g, 61 μmol) in 10 ml of CH_2Cl_2 was stirred with trifluoroacetic acid (10 ml) for 2 h. The solvent was removed by rotary evaporation and the residue dissolved in 3 ml H_2O and ultrafiltered (Amicon regenerated cellulose, YM1, NMWL 1000, wash with 30 ml pH 5 H_2O). The retentate was dried in vacuum to give a light brown residue: ^{1}H NMR (500 D_2O) 7.82 (s, T4 aromatic), 7.41 (s, T4

aromatic), 4.29 (bs, α), 3.00 (bs, ε), 2.13-1.70 (m, β, δ, γ); MALDI-MS gives a range T4-Lys_{4-11} **(SEQ ID NO: 19)**.

Marked up version of the paragraph on page 65, lines 24-25, is below:

T4-Trp_{15}: **(SEQ ID NO: 20)** ^{1}H NMR (500 DMSO) 8.25-6.80 (m, aromatic), 4.50 (bs, α), 3.40 (bs, β), 3.00 (bs, β).

Marked up version of the paragraph on page 66, lines 3-11, is below:

To T4 (0.078 g, 100 μmol) in 10 ml dry DMF was added Trp(Boc)NCA (0.500 g, 1.514 mmol). After stirring for 64 h under Ar the reaction was quenched by adding 30 ml H2O. The cloudy white solution was chilled to 4° C, centrifuged and the pellet washed three times with 25 ml H2O. The residue was dried in vacuum to provide **(SEQ ID NO: 20)** $Trp(Boc)_{15}$-T4 as a brown solid. This material was further purified by ultrafiltration (Amicon regenerated cellulose, YM1, NMWL 1000, wash with 30 ml pH 5 H_2O) to provide **(SEQ ID NO: 20)** $[Trp(Boc)]_{15}$-T4 as a brown-gold solid (0.400 g, 79%): ^{1}H NMR (500 DMSO) 8.25-6.80 (m, aromatic), 4.50 (bs, α), 3.40 (bs, β), 3.00 (bs, β), 1.50 (bs, t-Bu).

Marked up version of the paragraph on page 66, lines 12-15, is below:

To **(SEQ ID NO: 20)** $[Trp(Boc)]_{15}$-T4 (0.509 g) in 8 ml of 1:1 CH_2Cl_2: trifluoroacetic acid was stirred for 1.5 h. The solvent was removed by rotary evaporation and the residue dried in vacuum to yield a brown solid (0.347 g, 97%): ^{1}H NMR (500 DMSO) 8.25-6.80 (m, aromatic), 4.50 (bs, β), 3.40 (bs, α), 3.00 (bs, β).

Marked up version of the paragraph on page 66, lines 17-18, is below:

(SEQ ID NO: 18) $[Lys(Boc)]_{15}$-T4: ^1H NMR (500 D_2O) 7.82 (s, T4 aromatic), 7.41 (s, T4 aromatic), 4.29 (bs, α), 3.00 (bs, ε), 2.13-1.70 (m, β, δ, γ).

Marked up version of the paragraph on page 66, lines 20-21, is below:

(SEQ ID NO: 18) Lys_{15}-T4: ^1H NMR (500 D_2O) 7.82 (s, T4 aromatic), 7.41 (s, T4 aromatic), 4.29 (bs, α), 3.00 (bs, ε), 2.13-1.70 (m, β, δ, γ).

Marked up version of the paragraph on page 67, lines 4-9, is below:

To the random T4/$[Trp(Boc)]_{15}$ **(SEQ ID NO: 20)** polymer was added 10 ml 1:1 CH_2Cl_2: trifluoroacetic acid and the reaction stirred for 1 h. The solvent was removed by rotary evaporation to provide the deprotected polymer as a brown solid (0.262 g, 91%) which was further purified by ultrafiltration (Amicon regenerated cellulose, YM1, NMWL 1000, wash with 30 ml pH 5 H_2O): ^1H NMR (500 DMSO), 8.25-6.80 (m, aromatic), 4.50 (bs, α), 3.40 (bs, β), 3.00 (bs, β).

Marked up version of the paragraph on page 67, lines 11-12, is below:

Random T4/Lys_{15} **(SEQ ID NO: 18)**: ^1H NMR (500 D_2O); 7.82 (s, T4 aromatic), 7.41 (s, T4 aromatic), 4.29 (bs, α), 3.00 (bs, ε), 2.13-1.70 (m, β, δ, γ).

Marked up version of the paragraph on page 67, lines 23-25 through page 68, lines1-6, is below:

To Lys_{14} **(SEQ ID NO:10)** HBr (0.106 g, 37 μmol) in 0.8 ml H_2O pH 8 was added the valproic succinimidyl ester (0.104 g, 431 μmol) dissolved in 0.4 ml THF. The reaction was stirred overnight whereupon 8 ml H_2O was added. The mixture was acidified to pH 3 with 6 M HCl and extracted twice with 2 ml CH_2Cl_2. The aqueous layer was dried and the residue dissolved in 1 ml H_2O. The solution was purified by SEC (G-15, 10 ml dry volume) and eluted with water. Those fractions containing conjugate were combined and dried to yield a white solid (0.176 mg) which by NMR indicated 28 Lysine **(SEQ ID NO: 21)** for every one drug molecule; ^1H NMR (D_2O) 4.29 (m, 1H, α), 3.00 (m, 2H, ε), 1.87-1.68 (m, 4H, β, δ), 1.43 (m, γ, methylene), 0.85 (t, methyl).

Marked up version of the paragraph on page 68, lines 9-14, is below:

(SEQ ID NO: 8) $AcNGlu_{15}$ $(3\text{-mevastatin})_2$

To $polyGlu_{15}$ **(SEQ ID NO: 8)** (0.116 g, 69 μmol) in 3 ml dry DMF was added 1 ml pyridine and acetic anhydride (20 μl, 207 μmol). After stirring for 21 h the mixture was acidified with 6 N HCl until pH 1 and then cooled to 4° C. The white precipitate was collected by centrifugation and washed three times with H_2O and then dried under vacuum to yield 11 mg of N-acetylated $polyGlu_{15}$ **(SEQ ID NO: 8)**.

Marked up version of the paragraph on page 68, lines 15-25 through page 69, lines 1-5, is below:

To N-acetylated polyGlu$_{15}$ **(SEQ ID NO: 8)** (0.011 g, 7 α mol) in 4.8 ml dry DMF was added dicyclohexylcarbodiimide (0.022 g, 108 μmol). After stirring twenty minutes the heterogeneous solution was filtered to remove insoluble dicyclohexylurea and combined with mevastatin (0.042 g, 108 μmol) and N-dimethyl-4-aminopyridine (0.013 g, 108 μmol). The mixture stirred for 23 h whereupon the reaction was quenched by the addition of 20 ml H_2O. The solution was extracted twice with 10 ml $CHCl_3$. The aqueous component was adjusted to pH 3 with 1 N HCl and cooled to 4° C. The resultant white precipitate was isolated by centrifugation and washed three times with 8 ml H_2O. The solid was dissolved in 1 ml H_2O and washed with 1 ml CH_2Cl_2 and twice with 2 ml EtOAc. The aqueous layer was acidified to pH 3 with 1 N HCl, cooled to 4° C, the precipitate isolated by centrifugation and washed twice with 2 ml H_2O. The dried conjugate (2 mg) was shown by ^{1}H NMR to contain fifteen Glu **(SEQ ID NO: 8)** for every two mevastatin molecules: ^{1}H NMR (500 MHz, DMSO) 5.92 (5' mevastatin), 5.72 (3' mevastatin), 5.19 (4' mevastatin), 5.17 (8' mevastatin), 5.12 (3 mevastatin), 4.41 (5 mevastatin), 4.03 (α, Glu), 2.25 (γ, Glu), 1.88 (β, Glu), 0.82 (4",2' allylic methyl mevastatin), 1.17 (2" mevastatin).

Marked up version of the paragraph on page 68, lines 15-25 through page 69, lines 1-5, is below:

(SEQ ID NO: 8) Glu$_{15}$ (3-mevastatin) (160)

To Glu$_{15}$ **(SEQ ID NO: 8)** (0.151 g, 77 μmol) in 3 ml dry DMF was added dicyclohexylcarbodiimide (0.239 g, 1.159 mmol) and the reaction stirred for 4 h under Ar.

The white precipitate was removed and N-dimethyl-4-aminopyridine (0.141 g, 1.159 mmol) and mevastatin (0.222 g, 0.569 mmol) were added dissolved in 10 ml $CHCl_3$. The reaction stirred for 21 h under Ar whereupon the precipitate was removed. The solution was concentrated by rotary evaporation and added to 40 ml saturated NaCl (aq) adjusted so pH 8. The homogeneous solution was extracted three times with 20 ml CHCl3 and then ultrafiltered (Amicon regenerated cellulose, YM1, NMWL 1,000). The retentate was dried in vacuum to yield 8 mg of a white residue which showed a ratio of 15 Glutamic **(SEQ ID NO: 8)** acids to one mevastatin by ^1H NMR (500 D_2O); 5.92 (5' mevastatin), 5.72 (3' mevastatin), 5.19 (4' mevastatin), 5.17 (8' mevastatin), 5.12 (3 mevastatin), 4.41 (5 mevastatin), 4.03 (α, Glu), 2.25 (γ, Glu), 1.88 (β, Glu), 0.82 (4",2' allylic methyl mevastatin), 1.17 (2" mevastatin).

Remarks

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

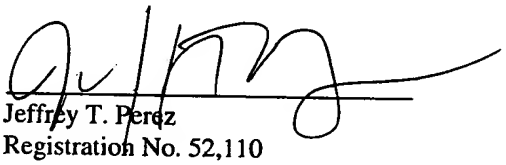
No additional fees are believed to be necessary in connection with the filing of this paper. However, in the event any fees are necessary, the Commissioner is hereby authorized to charge Deposit Account 50-0206 for any such fees.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

HUNTON & WILLIAMS

Dated: April 23, 2003

By: 

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